# Studies on the Postoperative Local Adjuvant Chemotherapy for Esophageal Carcinoma, Especially the Infusion of Bleomycin into the Thoracic Duct

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# Studies on the Postoperative Local Adjuvant Chemotherapy for Esophageal Carcinoma, Especially the Infusion of Bleomycin into the Thoracic Duct

by

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## Introduction

Hitherto, the postoperative treatment of esophageal carcinoma has been mainly performed by the T-shaped irradiation to the cervical and the upper mediastinal regions or by the adjuvant chemotherapy. It is worthy of note that a large number of recurrences occurred in the lymphnodes in these regions[1)14)29)30)]. To cope with these lymphnode metastases, especially in the upper mediastinum and on the opposite side of the thoracotomy, the author experimentally tried the method by which Bleomycin (BLM) was infused continuously into the thoracic duct in the normal and the opposite directions of the lymph flow, and tried to improve the remote results of operation for esophageal carcinoma.

The measurement method of the concentration of BLM.

In these experiments, the concentration of BLM in various body fluids and organs were determined by bioassay, the Band Culture method by OKUBO[25)]. The strain of test organism : bacillus subtilis PCI-219. Number of organisms : $2.1 \times 10^7$ml. Medium : MÜLLER-HINTON medium. Incubation time (37°C) : 5—8 hours. Minimum inhibition concentration : 0.25mcg/ml.

Blood and lymph were centrifuged at 2000 rpm for 5 minutes, and their supernatant fluids were used for the measurement. In order to determine BLM concentration in the organs, the animals were sacrificed by exsanguination, their resected tissues were homogenized into an emulsion and diluted with the physiological saline solution twice the volume as that of the homogenates. These homogenates were kept in a refrigerator at 4°C for 24 hours. These supernatant fluids were used for the measurement of BLM concentration.

Key words : Bleomycin, Esophageal cancer, Adjuvant chemotheraphy, Infusion, Thoracic duct.
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*Chapter* 1. *Distribution of BLM after intramucal injection of BLM solution into the isolated esophagus.*

Materials and methods : Adult mongrel dogs weighing about 10 kg were anesthetized by intravenous injection of Nembutal and the respiration was controlled by the intratracheal intubation with AIKA's pressure-preset respirator with room air. Right thoracotomy was carried out through the 6th intercostal space and a cutdown tube was inserted from the external jugular vein into the azygos vein to collect blood. The thoracic duct was exposed in the left supraclavicular region and inserted with a 21 G elastic needle to collect lymph. Thereafter, the femoral vein was also cannulated with a cutdown tube to draw bood and infuse it with the physiological saline solution. The thoracic esophagus was then isolated and its own arteries, veins and lymph ducts, except for the azygos vein, were completely divided. Four mg per ml solution of BLM was injected into the submucosal layers of the middle thoracic esophagus in the dogs at a dose of 2mg/kg. BLM concentrations in the femoral vein blood, the azygos vein blood and the thoracic duct lymph during 30 minutes after injection, and those in the esophagus, the regional lymphnodes and others were measured.

These results were compared with the normal control values[37].

Results : When BLM solution was injected into the middle thoracic esophagus of the normal control cases, BLM concentration amounted to a peak level 15 minutes after injection and then decreased gradually in the azygos vein blood and the thoracic duct lymph. On the other hand, in the cases with the isolated esophagus, the curve showed the same trend except that the concentration in the thoracic duct lymph amounted to a peak level 40 minutes after injection. But the BLM concentration reduced by half in the azygos vein blood (Fig. 1). BLM levels in each portion of the esophagus 30 minutes after the submucosal injection showed the highest values in the injected portion. Especially, in the cases

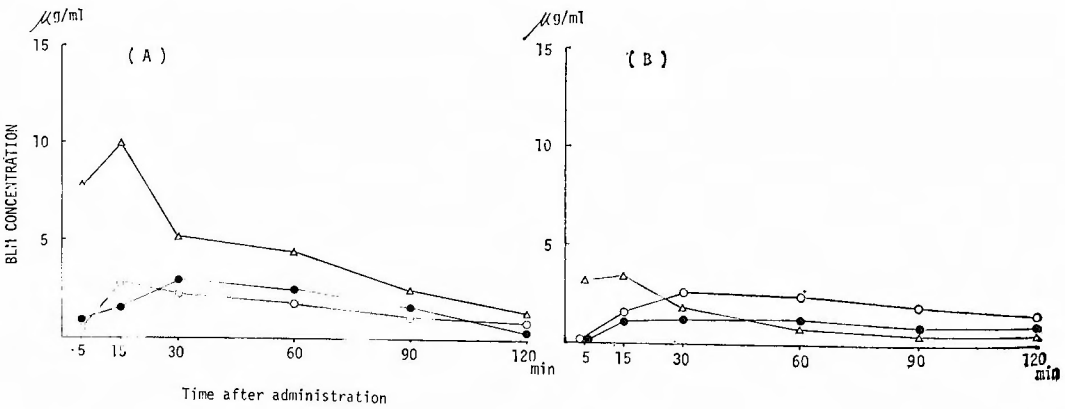


**Fig.** 1. BLM levels in blood and lymph following intramural injection of 2mg/kg of BLM into the middle thoracic esophagus of dogs. A) Normal control case. B) Case with the isolated esophagus. △—△ azygos vein, ●—● femoral vein, ○—○ thoracic duct lymph.

with the isolated esophagus, it was noted to be several times as much as the normal control values and spread well into the portions oral and aboral to the injected portion (Fig. 2). BLM concentration in the regional lymphnodes 30 minutes after injection is shown in Fig. 3. In the normal control cases, it showed high levels in the thoracic regional lymphnodes

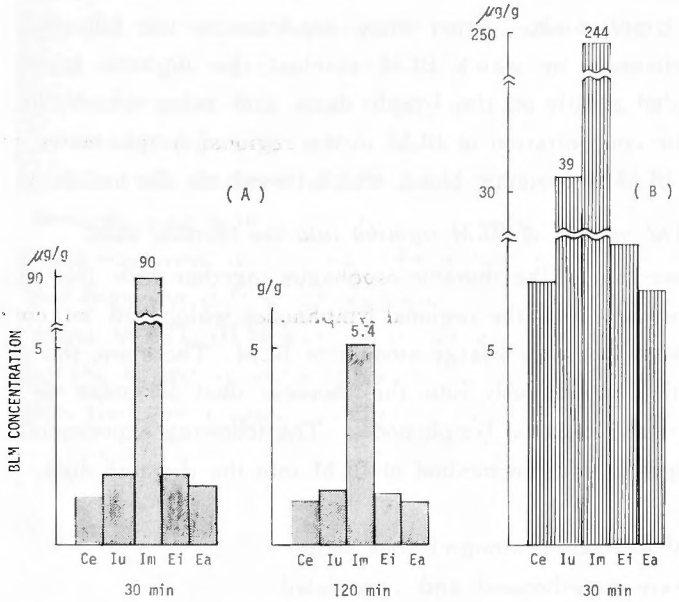


**Fig. 2.** BLM levels in each portion of esophagus 30 min after intramural injection of 2mg/kg of BLM into the middle thoracic esophagus of dogs. A) Normal control case. B) Case with the isolated esophagus. Ce : Cervical esophagus, Iu : Upper thoracic esophagus, Im : Middle thoracic esophagus, Ei : Lower thoracic esophagus, Ea : Abdominal esophagus.

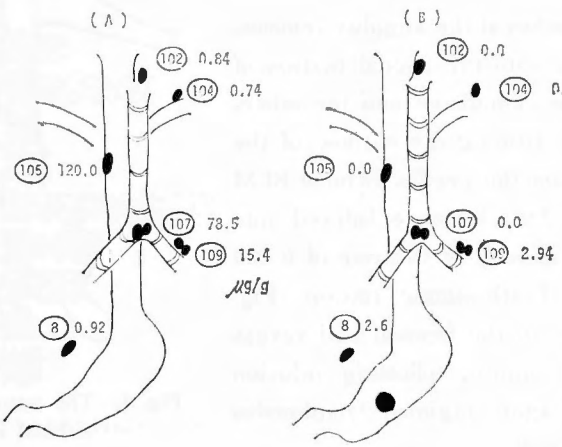


**Fig. 3.** BLM concentration in the regional lymph nodes 30 minutes after intramural injection of 2mg/kg of BLM into the middle thoracic esophagus. Number of regional lymph node : Carcinoma of the esophagus, descriptive rules in the clinic and pathology. A) Normal control case. B) Case with the isolated esophagus.

but only a slight amount in the cervical and abdominal lymphnodes. In the cases with the isolated esophagus, BLM was not detected in the thoracic regional lymphnodes. But, in No. 8 (the abdominal regional lymphnode), it showed a relatively high level as compared with the former. When BLM solution was injected into the submucosal layer of the esophagus, it spread toward the oral and aboral portions of the esophagus and was carried to the regional lymph nodes. From these experiments, the following conclusions were obtained. The channels by which BLM reached the regional lymph nodes from the esophagus depended greatly on the lymph ducts and veins which flowed out from the esophagus that the concentration of BLM in the regional lymph nodes was little affected by the absorbed BLM in systemic blood, which flowed via the nutritional arteries.

*Chapter 2. The method of BLM infusion into the thoracic duct.*

After the dissection of the thoracic esophagus together with the carcinoma lesion, it was difficult to presume that the regional lymphnodes which had no connection with the esophagus were supplied with a large amount of BLM. Therefore, the author attempted to infuse BLM solution continuously into the thoracic duct in order to distribute a large amount of BLM to the regional lymph nodes. The following experiments were performed.

1. The retrograde infusion method of BLM into the thoracic duct. (RIT)

Materials and methods : Mongrel dogs weighing 10—15 kg were anesthetized and cannulated in the femoral and azygos veins with a cutdown tube by the above-mentioned method. Thereafter the thoracic duct was exposed in the left supraclavicular region of dogs to be inserted with a 21 G elastic needle. When the thoracic duct was divided into three or four branches at the angulus venosus, the needle was inserted into the caudal portion of the division, or one was cannulated and the others were ligated. After confirming the outflow of the thoracic duct lymph from the needle, 10 ml of BLM solution at the dose of 2 mg/kg were infused into the thoracic duct continuously at the rate of 0.094 ml per minute with a Truth atomic infusor (Fig. 4). BLM concentrations in the femoral and azygos vein blood during 120 minutes following infusion and those in the esophagus, regional lymphnodes and others were measured.

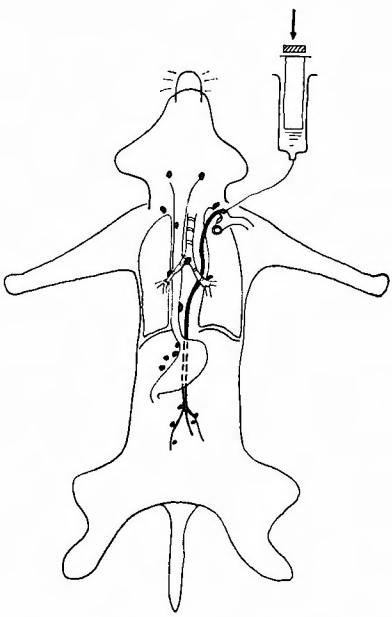

**Fig. 4.** The retrograde infusion method of BLM into the thoracic duct.

2. The infusion method of BLM into the posterier mediastinum. (IM)

In 1977, INOGUCHI reported on the efficiency of the infusion of BLM emulsion into the

posterior mediastinum[16]. The following experiment was performed to compare RIT with IM under the same condition.

Materials and methods : Mongrel dogs weighing 10—15 kg were anesthetized by the above-mentioned method. Right thoracotomy was carried out through the 5th intercostal space in dogs. A cutdown tube was inserted from the left supraclavicular region into the posterior mediastinum and the tip was fixed near the level of the bifurcation of the trachea. Thereafter, the solution of BLM began to infuse in the same quantity and at the same rate as those of RIT. BLM concentration in each blood and lymph during 120 minutes after the infusion and that in each organs were also measured.

1. and 2. Results : In 1965, BRZEK et al reported that he tried the retrograde lymphangiography of the thoracic duct with 10—20 ml of Urografine in 20 cases of various pulmonary diseases and succeeded in 10 cases[5]. We performed the retrograde infusion into the thoracic duct in 9 dogs, but it failed in one case on account of the complete obstruction by valves. In the group of RIT, BLM levels in the azygos vein blood arrived at a peak level 15 minutes after the beginning of the infusion and decreased gradually thereafter. In the femorel vein blood the peak appeared 30 minutes after the start of the infusion. In the

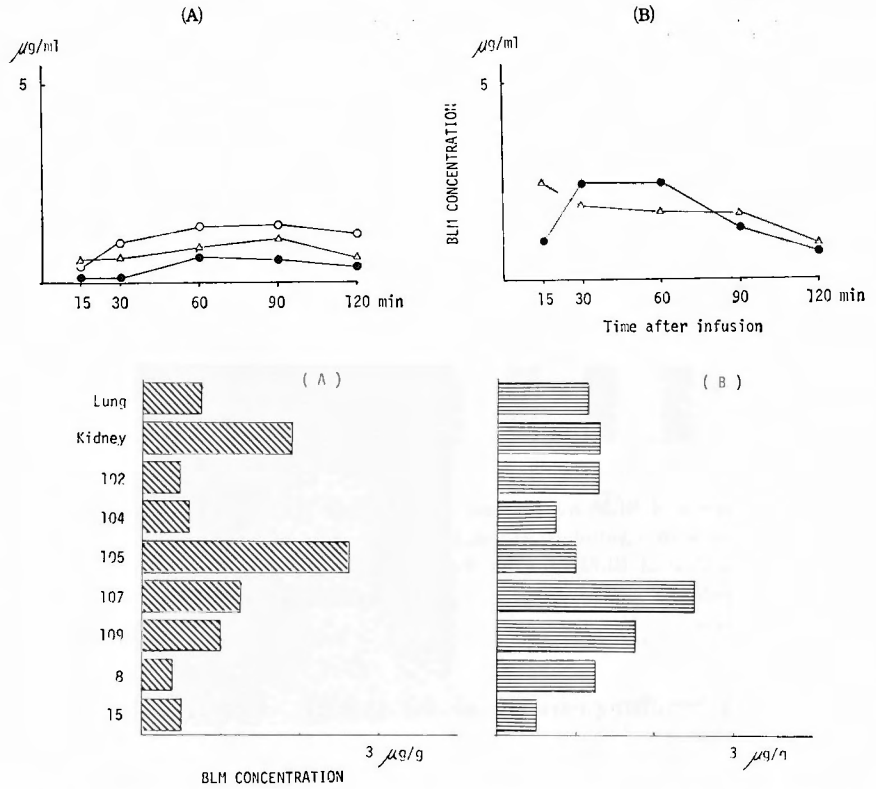


**Fig. 5.** BLM levels in blood, lymph and the regional lymph nodes following the infusion of 10 ml of BLM solution at the dose of 2 mg/kg into the thoracic duct in the left supraclavicular region (A) and into the posterior mediastinum (B) at the rate of 0.094 ml/min with a Truth atomic infusor. △—△ azygos vein, ●—● femoral vein, ○—○ thoracic duct lymph.

group of IM, BLM levels in the lymph and the femoral and azygos vein blood arrived at a peak level 90 minutes after the start of the infusion. As to BLM levels in the regional lymphnodes, it showed a tendency to be higher in RIT. Especially in No. 107 lymphnodes, the BLM levels in RIT increased twofold over that in IM. BLM concentrations in lungs in both groups were so low that there was no difference (Fig. 5). BLM levels in both groups in each portion of the esophagus showed the highest level in the middle thoracic esophagus and spread well to the oral and aboral.

The difference of BLM distribution in each layer of the esophageal wall in both groups is shown in Fig. 6. In the group of RIT, BLM was found in large amounts in the mucosal and submucosal layers, while in the group of IM it was detected mostly in the muscular layer. These results were thought to be attributed to the fact that BLM solution came in contact directly with the adventitia of the esophagus in the group of IM, while in the group of RIT, BLM solution flowed back from the thoracic duct into the regional lymphnodes and passed through the esophageal muscular layer into the mucosal and submucosal layers in which the rich network of lymphatics was present.

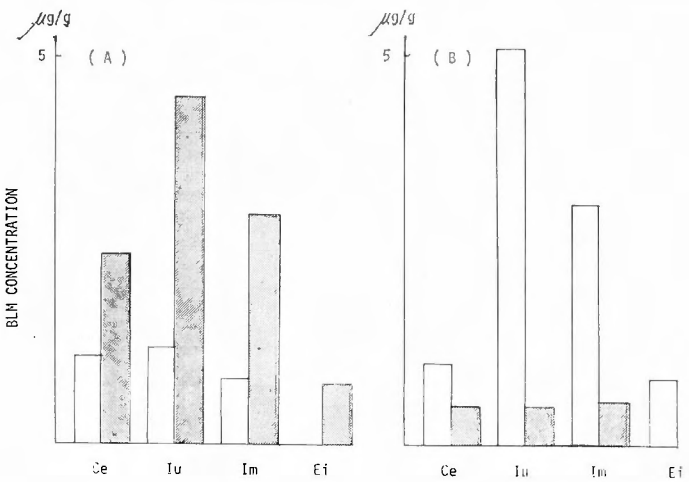


**Fig. 6.** The difference of BLM distribution in each layer of the esophageal wall following the infusion with 10ml of BLM solution at the dose of 2mg/kg. A) The retrograde infusion method of BLM into the thoracic duct. B) The infusion method of BLM into the posterior mediastinum. ☐ the mucosal and submucosal layers, ⁙ the muscular layer.

3. The retrograde lymphangiography of the thoracic duct and the pressure of the terminal thoracic duct[5)6)].

In order to prove the above results, Lipiodol was infused retrogradely into the thoracic duct from the portion of angulus venosus with a Truth atomic infusor. The roentgenogram was taken and the pressure in the terminal thoracic duct during the infusion of Lipiodol was measured.

Materials and method. : Mongrel dogs weighing 13 — 15 kg were anesthetized by the above-mentioned method. In the left supraclavicular region of dogs, a 21 G elastic needle was cannulated into the thoracic duct.

A three direction cock was connected to the tip of the needle, one of which was set for the infusion of Lipiodol and the other was set for the measurement of the pressure of the terminal thoracic duct. The monometer was prepared from 0 to 150 $cmH_2O$ and the baseline was placed at the level where an elastic needle was cannulated. The pressure of the terminal thoracic duct was 7 $cmH_2O$ at the expiratory time before the infusion of Lipiodol. The Lipiodol began to infuse at the rate of 0.094 ml per minute. The roentgenogram was taken by the portable X-ray photography installation and the pressure of the terminal thoracic duct was measured by the saline-manometer during the infusion of Lipiodol. The condition of the X-ray photography was 100 kpv, 10 mA, 0.1 sec, 30 cm, Neopan SS.

Results : The retrograde flow of Lipiodol into the regional lymphnodes in the upper mediastinum was observed on a roentgenogram and the pressure of the terminal thoracic duct was found to be 23 $cmH_2O$ when 5 ml of Lipiodol was infused and with the infusion of 10 ml of Lipiodol the pressure amounted to over 40 cm $H_2O$ and the shadow of the regional lymphnodes in the upper mediastinum became thick. Furthermore, the retrograde flow into the capillary lymphatics in the lungs was observed (Fig. 7).

This Lipiodol in the capillary lymphatics in the lungs still remained 2

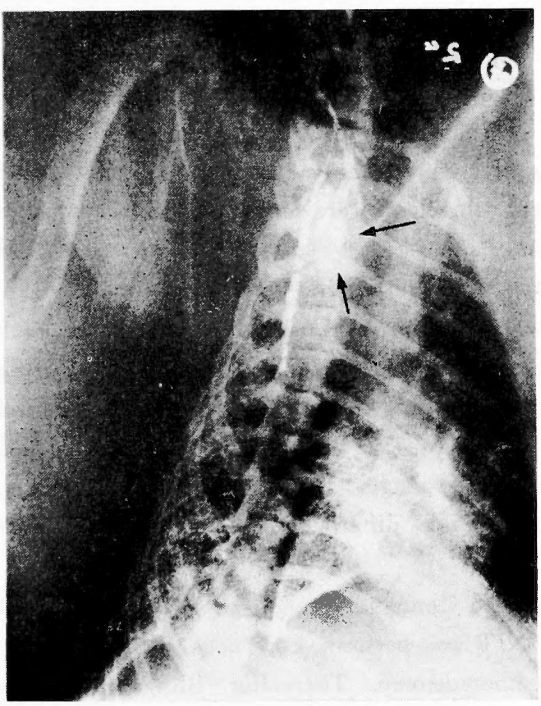

Fig. 7. The retrograde lymphagiography of the thoracic duct. The picture shows that the regional lymph nodes in the upper mediastinum are observed on a roentgenogram with the infusion of 5 ml of Lipiodol.

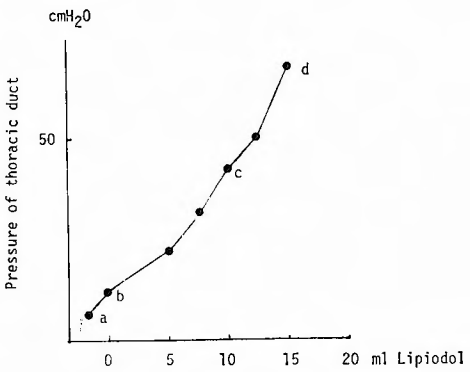


Fig. 8. The pressure of the terminal thoracic duct following the retrograde infusion of Lipiodol into the thoracic duct at the rate of 0.094 ml per minute. (a) Before the saline transfusion into the femoral vein. (b) 30 minutes after saline transfusion at the rate of 100 ml per hour. (c) 100 minutes after the beginning of Lipiodol infusion. (d) 150 minutes after the beginning of Lipiodol infusion.

hours after the completion of the infution. With the infusion of 15 ml of Lipiodol (150 minutes after the beginning of the infusion), the pressure had mounted to 70 cm$H_2O$ (Fig. 8).

4. The normograde infusion method of BLM into the thoracic duct. (NIT)

With the retrograde infusion method of BLM into the thoracic duct, the pressure of the thoracic duct extremely elevated because the flow of the BLM solution went against the physiological flow of the thoracic duct lymph and the valves in the thoracic duct offered the resistance[18] Taking these points into consideration the solution of BLM was slowly infused into the segment of the thoracic duct which was ligated in the supraclavicular and supradiaphragmatic portions.

Materials and methods : Mongrel dogs weighing 10 — 15 kg were anesthetized by the above-mentioned method. Firstly, the thoracic duct was ligated in the left supraclavicular portion. Secondly, the dog was layed down in the left lateral position, and right thoracotomy was carried out through the 5th or the 6th intercostal space. Thereafter, in the supra-diaphragmatic region, the thoracic duct was separated, which ran dorsal to the lower thoracic esophagus. In dogs weighing 10—15 kg, the thoracic duct ranged from 2 to 3mm in the outer diameter in the supradiaphagmatic region. Its exposure and the cannulation with a 21 G elastic needle were easy to perform. The thoracic duct was ligated once more 1 cm caudal to the point of insertion. Five ml of the solution of BLM at the dose of 2 mg/kg was infused into the thoracic duct at the rate of 0.049 ml per minute with a Truth atomic infusor. BLM levels in the azygos and femoral vein blood were measured for 2 hours after the infusion. After 2 hours, the dogs were sacrificed by exsanguination and BLM concentrations in the esophagus, regional lymphnodes and others were measured.

Results : With NIT, BLM levels in the azygos and femoral vein blood reached the peak 30 minutes after the beginning of the infusion, but thereafter it remained constant during 2 hours. BLM concentrations in the regional lymphnodes are shown in Fig. 9. It showed the extreme high levels in contrast with IM and RIT. The BLM levels in the esophagus were high in the upper two-thirds of the thoracic esophagus. In the lungs and the kidneys, they remained at low levels and showed no noticeable difference as compared with the former two groups.

Next, in order to examine under the condition similar to the postoperative period of the clinical cases with esophageal carcinoma, NIT was performed in dogs after cleansing of the regional lymphnodes on the side of the thoracotomy. Thereafter, BLM distribution in the regional lymphnodes on the opposite side of the thoracotomy was measured.

Result : In spite of the anticipation that the devastation and the opening of the lymph ducts might occur after the cleansing of the regional lymphnodes on the side of the thoracotomy, BLM levels were detected at high levels in the regional lymph nodes on the opposite side of the thoracotomy with NIT (Table 1).

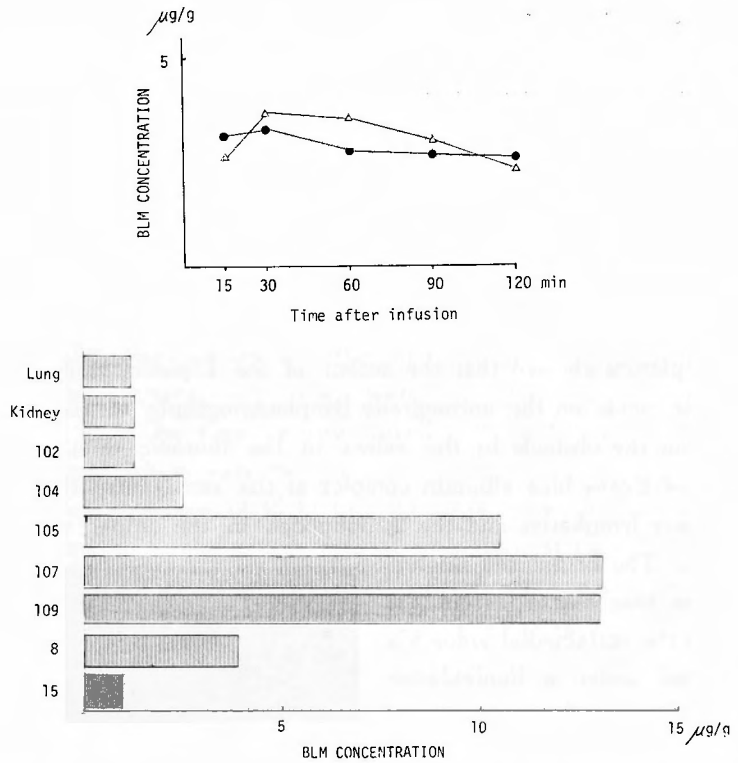


**Fig.** 9. BLM levels in blood and the regional lymphnodes following the infusion of 10 ml of BLM solution at the dose of 2mg/kg by the normograde infusion into the thoracic duct. △—△ azygos vein, ●—● femoral vein.

**Table** 1. The BLM concentration in the lymphnodes on the opposite side of thoracotomy when the NIT was performed in dogs after the cleansing of the regional lymphnodes on the side of thoracotomy.

| | 107 1/2, 109 R | 107 1/2, 105 |
|---|---|---|
| Lung | 1.5 | 1.9 |
| Kidney | 1.0 | 1.5 |
| 102 | 2.7 | 3.0 |
| 104 | 3.0 | 2.1 |
| 105 | 14.4 | — |
| 107 | 20.0 | 11.0 |
| 108 | 3.7 | 2.1 |
| 109 | 12.4 | 10.0 |

**Table** 2. Number of the regional lymph nodes in Fig. 3, 9, 12 and Table 1.

| | |
|---|---|
| 102 | : Deep cervical lymph node |
| 104 | : Supraclavicular lymph node |
| 105 | : Upper thoracic paraesophageal lymph node |
| 107 | : Bifurcation lymph node |
| 108 | : Middle thoracic paraesophageal lymph node |
| 109 | : Pulmonal hilar lymph node |
| 8 | : Common hepatic artery lymph node |
| 15 | : Middle colic artery lymph node |

5. The method of the normograde lymphangiography of the thoracic duct and the infusion with Evans blue.

With the same method as NIT, the dogs were infused with 5 ml of Lipiodol into the

thoracic duct and a roentgenogram was taken during the infusion. In the same manner, other dogs were infused with 5 ml of the Evans blue albumin complex into the thoracic duct, which was prepared by dissolving 0.6 g of Evans blue and 4 g of bovine serum albumin in 100 ml of normal saline, which was shown by NICOLYSEN and STAUB[23]. After 2 hours, the dogs were sacrificed by exsanguination and the regional lymphnodes and others were resected. The specimens were frozen in dry ice acetone and then freeze-dried at −35°C for 4 days. The distribution of the bright red Evans blue albumin fluorescence was studied on 6$\mu$m thick section under a Olympus FLM fluorescence microscope (excitation filter : B2, Barrier filter Y52).

Results : The picture showed that the ascent of the Lipiodol reached the portion of the ligation in the neck on the normograde lymphangiography of the thoracic duct by NIT. It ran without the obstacle by the valves in the thoracic duct (Fig. 10). On the infusion with 5 ml of Evans blue albumin complex at the same rate, the Evans blue was found in the capillary lymphatics and the lymphnodes in the upper mediastinum at the end of the infusion. The bright red fluorescence due to Evans blue reached from the sinus marginalis to the intramedial sinus via the cortex, observed under a fluorescence microscope (Fig. 11).

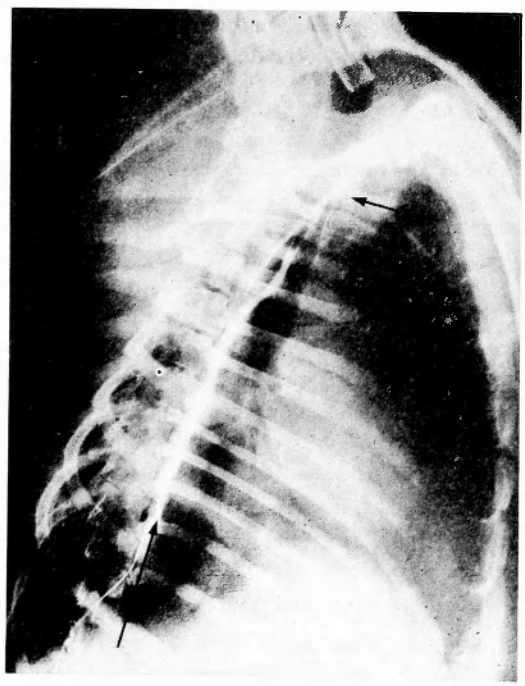

Fig. 10. The roentgenogram of the normograde lymphagiography of the thoracic duct with the infusion of 5 ml of Lipiodol.

Fig. 11. The histology showed that Evans blue reached from the sinus marginalis to the intramedial sinus via the cortex in the observation under a fluorescene microscope (×100).

By the method of NIT a large quantity of BLM arrived at the regional lymphnodes of the esophagus. In addition, BLM levels in the lungs were very low. From the viewpoint of this result, it was thought to be useful in the postoperative local chemotheraphy for esophageal carcinoma.

*Chapter 3. Local injection of BLM solution into the submucosa of the cervical esophageal fistula*[28].

Materials and methods : Cervical esophageal fistula was constructed in the left cervical region following transection of the cervical esophagus at the level of the thoracic inlet in dogs. BLM of 2 mg/kg was injected into the submucosa of the esophageal fistula. BLM levels in the azygos and femoral vein blood were measured for one hour following the injection. After one hour, the dogs were sacrificed and BLM levels in the esophagus and regional lymphnodes and others were measured.

Results : With local injection of BLM into the submucosa of the cervical esophageal fistula, BLM concentration in the azygos vein blood arrived at the peak 10 minutes after the injection and thereafter gradually decreased. BLM was usually detected in a small amount in the femoral vein blood. BLM levels in the esophagus were detected at high levels in the injected portion of the cervical esophagus, moreover in both mucosal and muscular layers. BLM levels were also detected in the upper thoracic, in the middle thoracic and in the lower thoracic esophagus, in the order mentioned, especially that was

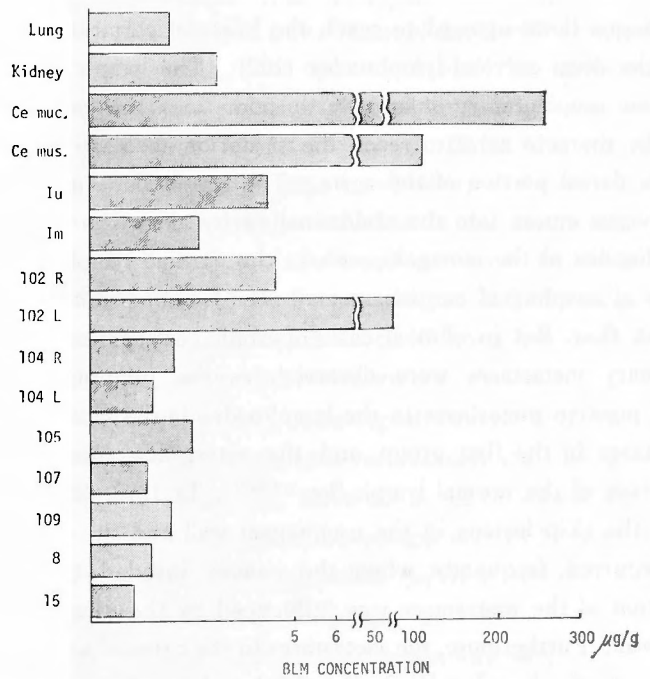


**Fig. 12.** BLM levels in the regional lymphnodes, esophagus and other organs 60 minutes after intramural injection of 2mg/kg of BLM into the cerivical esophageal fistula of dogs.

detected at a high level in the mucosa. The distribution of BLM was found at high levels in the cervical lymph nodes and in a small amount in the thoracic lymph nodes, such as No. 105, No. 107 and No. 109. BLM concentrations in the lungs remained at a low level (Fig. 12). From these results, this method was thought to be effective on the cases of the multistage operation and the cases with the unresectable esophageal carcinoma.

## Discussion

The lymphnode metastases of esophageal carcinoma have been one of the important factors that deteriorated the remote result of operation for esophageal carcinoma[1)14)22)28)29)]. In 1974, IDE[14)] reported that metastases to the lymphnodes were found in 70% of their resectable cases of the thoracic esophageal carcinoma, and 75 out of 87 cases who had the positive metastases to the lymphnodes had metastases to the regional lymphnode in the second and third groups[7)17)]. KUSUNA[18)] and MORI[20)] reported in detail on the anatomy of the esophageal lymphatic system. According to their studies, the lymph ducts in the esophagus flowed from the networks of capillary lymphatics in the lamina propria mucosae, especially immediately above the lamina mucosae or below the epithelial lining flow through the submucosa along the longitudinal axis of the esophagus for a long distance and passed through the muscular layer at right angles to reach the regional lymphnodes, while the lymph ducts which branched out of the networks of capillary lymphatics in the muscular layer arrived directly at the segmental lymphnodes.

As to the normal lymph flow in the esophageal wall, that in the upper one third of the thoracic esophagus flows upward to reach the bilateral cervical paraesophageal lymphnodes (101) and the deep cervical lymphnodes (102). The lymph flow in the middle one third of the thoracic esophagus runs laterally to pour into the parabronchial lymphnodes and run around the thoracic aorta to reach the posterior mediastinal lymph nodes which are situated in the dorsal portion of the aorta. The lymph flow in the lower one third of the thoracic esophagus enters into the abdominal cavity along the esophagus to pour into the regional lymphnodes of the stomach, such as the cardiac lymphnodes. The metastases to the lymphnodes of esophageal carcinoma may occur in conformity to the above-mentioned physiological lymph flow. But in clinical cases of esophageal carcinoma frequent occurrence of such extraordinary metastases were observed, as the jumping metastases which are recognized as the positive metastases to the lymphnodes in the second and the third groups without the metastases in the first group, and the retrograde metastases which occur in the opposite direction of the normal lymph flow[1)7)9)29)]. In 1972, ISHIGAMI[17)] reported on his clinical cases that the skip lesions in the esophageal wall and the extensive metastases to the lymphnodes occurred frequently when the cancer invaded the submucosa, and the longitudinal direction of the metastases was influenced by the direction of the lymph flow in the esophageal wall. Furthermore, the metastases to the cervical and abdominal lymphnodes and the mestastases to the lymphnodes in the third and fourth groups increased when the intramural lymph flow of the esophagus was blocked by the preoperative irradiation or the

invasion throughout all layers of the esophageal wall[24]. Therefore, the metastases to the lymphnodes should be cleansed thoroughly, as much as possible, during radical operation for esophageal carcinoma which show the extensive and complicated metastases to the lymphnodes[1)9)14)29)30)]. But, in common cases, the cleansing of the regional lymphnodes has been limited only to those on the side of the thoracotomy, because it has been well known that the occurrence of the postoperative pulmonary complication has increased by the operative procedures of the cleansing of the lymphnodes in the upper mediastinum and on the opposite side of the thoracotomy. From this viewpoint, the development of the postoperative and preoperative irradiation and the adjuvant chemotherapy has been taken into serious consideration. BLM, which was discovered by UMEZAWA[31)] in 1966, showed a selective effect on the squamous cell carcinoma[11)12)]. WADA, firstly used the BLM for esophageal carcinoma, tried the preoperative adjuvant chemotherapy at a voluminous dose of 300 mg and found that BLM afforded a great relief to the esophageal tumor but some of the patients died of a serious pulmonary fibrosis due to the side effect of BLM[35)]. Thereafter, the method of the fractional injection of a small amount of BLM has been developed by SATO[27)] ans FUJIMAKI[8)]. At present, the combined treatment of radiation and BLM has been used ordinally to note the cooperation effects[2)3)8)36)]. Main side effects of BLM administration are fever, anorexia and the pulmonary complications which are most troublesome for the esophageal surgery. In 1975, one of our colleagues, SHIBATA[28)] studied on BLM concentration in the regional lymphnodes of the esophagus and the lungs following various methods of administration, BLM levels in the esophagus and intrathoracic regional lymph nodes increased following local injection into the esophageal wall, intravenous injection and selective intraarterial infusion, in the order mentioned, and the levels in the lungs were lowered following intravenous injection, selective intraarterial infusion and local injection, in the order mentioned. Therefore, local injection of BLM into the esophageal wall is advantageous for preventing the complication of pulmonary diseases. In 1978, one of our colleagues, YASUMOTO[37)] studied on local chemotherapy of the esophageal cancer, especially on BLM administration into the lumen of the esophagus with double balloon catheter. It showed the high distribution of BLM in the esophagus and the regional lymph nodes. Combining the intraluminal administration with BLM-Iontophoresis, the effect increased extremely as compared with the former method alone.

Local chemotheraphy of BLM for the esophageal cancer and the metastases to the regional lymph nodes have been performed with various methods, that is, intramural injection into the esophageal wall using endoscopy, infusion of BLM emulsion into the posterior mediastinum (by INOGUCHI[16)]), insertion of BLM-spongel and BLM injection into the key-station of No. 107 lymphnodes during the operation (by NAKAMURA[21)]) and insertion of solid BLM near the abdominal lymphnodes (by WATANABE[36)]).

On the other hand, as to the postoperative adjuvant chemotherapy for the esophageal carcinoma, it is difficult to distribute a large amount of BLM to the regional lymph nodes which had no connection with the esophagus after dissection of the thoracic esophagus

together with the carcinoma lesion. Therefore, the development of adjuvant chemotherapy for the metastases to the lymphnodes in the upper mediastinum and on the opposite side of the thoracotomy had been expected. When the author infused BLM solution continuously into the thoracic duct from this point of view, BLM distribution in the esophagus and the regional lymphnodes showed a high level. In spite of the anticipation that the devastation and the opening of the lymph channels might occur after the cleansing of the regional lymph nodes on the side of the thoracotomy, BLM levels were detected at high levels in the regional lymph nodes on the opposite side of the thoracotomy. With this method, BLM concentrations in the lungs remained at a low level as compared with local injection into the esophageal wall, so that it may contribute to prevent the lungs from the side effect. Furthermore, as BLM is inactivated more slowly in the course of time, it is suited for the continuous infusion.

According to the KUSUNA's studies[18] on the relation among the lungs, esophagus and thoracic duct, the following results were reported. The vas defferens of the bifurcation lymphnodes (107) pour into the bilateral pulmonary hilar lymph nodes (109), and thereafter vas defferens of the right pulmonary hilar lymphnodes enter into the right upper mediastinal lymphnodes via the right thoracic paratracheal lymph nodes (106) into which the lymph of the upper one third of the thoracic esophagus pour, and at last, end in angulus venosus. But vas defferens of the left pulmonary hilar lymph nodes pour into the arcus aortal lymph nodes and to the left thoracic paratracheal lymph nodes in which the lymph from the upper one third of the thoracic esophagus pour, and each vas defferens ends separatedly in the thoracic duct. The communication between the paratracheal lymph nodes and the deep cervical lymph nodes are found in 48% of the cases on the right side and in 21% on the left side in the Japanese. GRAY says many outflowing lymphatic ducts arrived at the thoracic duct in the mid-thoracic region, such as the lymph ducts from the intercostal region and vas defferens of the retromediastinal lymph nodes in which the lymph of the middle one third of the thoracic esophagus pour[10]. From these results, the following conclusions were obtained. BLM solution which was infused into the thoracic duct was firstly stagnated in the thoracic duct for a short period and secondly following the retrograde lymph flow reached the upper mediastinal and paratracheal lymphnodes, or directly arrived at the retromediastinal lymphnodes from the thoracic duct. As to the ligation of the thoracic duct, there has been various studies in the past. NOSE, in his experimental studies[24], attested that the lymph of the thoracic duct poured into the right angulus venosus through the new ways after the ligation of the left cervical thoracic duct in dogs, and mentioned the best countermeasure against the injury of the cervical thoracic duct was the ligation. According to INADOME's studies[15], the chyluria had not appeared when the thoracic duct was ligated at the level just above the diaphragm, and on the 17th day after the ligation collateral channel reached the upper thoracic duct. Experimentally, the establishment of callateral channels and lymphaticovenous shunts may also appear within two to three weeks after the ligation of the thoracic duct[19][38].

## Conclusion

To cope with the metastases to the lymphnodes, especially in the upper mediastinum and on the opposite side of the thoracotomy after operation for esophageal carcinoma, the author experimentally examined the method in which BLM was infused into the thoracic duct in the normal or opposite direction of the lymph flow. The results were as follows :

1) When BLM solution was injected into the wall of the esophagus, it appeared into the azygos vein blood in a great amount for a short time and then spread toward the oral and aboral portions of the esophagus by way of the intramural lymphatics and reached the regional lymphnodes in high concentration. In the cases with the isolated esophagus, BLM was also absorbed promptly into the azygos vein blood and well spread in the esophagus, but BLM was not detected in the thoracic regional lymphnodes, while a large amount of BLM remained in the esophageal wall for a long time. From these results, the following conclusion was obtained. The channels by which BLM reached the regional lymph nodes from the esophagus was largely due to the lymph ducts and veins which flowed out from the esophagus that the concentration of BLM in the regional lymphnodes was little affected by the absorbed BLM in systemic blood which flowed in via the nutritional arteries.

2) When Lipiodol was infused into the cervical thoracic duct in the opposite direction of the lymph flow, the thoracic duct and the lymph nodes in the upper mediastinum could be well observed in the roentgenogram. The pressure in the terminal thoracic duct during the infusion of Lipiodol amounted to over 40 $cmH_2O$.

3) When BLM solution was infused into the retromediastinal cavity at the level of the bifurcation of the trachea, BLM concentration in the regional lymph nodes of the esophagus showed a high level, while BLM was detected in lungs only in a trifling amount. In the esophagus, it was detected at a high level especially in the muscular layer.

4) When BLM solution was infused into the thoracic duct in the opposite direction of the lymph flow, BLM distribution in the regional lymphnodes showed a higher level as compared with that in the group of infusion into the retromediastinum, and also BLM in the lungs remained at a low level as compared with the retromediastinal group. BLM in the esophageal wall was detected in a great amount, especially in the mucosa and the submucosa.

5) When the thoracic duct was ligated at the left cervical and supradiaphragmatic portions and Lipiodol was continuously infused into the segment between these ligating portions in the normal direction of the lymph flow, it could be infused smoothly without the resistance of valves, and the thoracic duct was well observed in the roentgenogram. On the infusion with Evans blue albumin complex, the regional lymphnodes were studied on a thick section under a fluorescence microscope. A large amount of Evans blue poured into the lymph nodes and reached from the sinus marginalis to the intermedial sinus.

6) When BLM solution was infused into the segment of the thoracic duct, BLM concentrations in the regional lymph nodes showed an extremely high levels in contrast

with the former. After the cleansing of the lymphnodes on the side of the thoracotomy, BLM levels in the regional lymphnodes on the opposite side of the thoracotomy were detected at high levels.

7) When the cervical esophageal fistula was constructed in the left cervical region following transection of the cervical esophagus at the level of the thoracic inlet, BLM solution was injected into the submucosa of the fistula. BLM was detected at a high level in the cervical lymph nodes and in a small amount in the regional lymph nodes of the thoracic esophagus.

From these experiments, it became clear that the normograde and retrograde infusion methods of BLM into the thoracic duct and local injection of BLM into the cervical esophageal fistula were useful for the postoperative local adjuvant chemotherapy for esophageal carcinoma.

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和文抄録

# 食道癌術後局所制癌剤療法に関する基礎的研究，とくに胸管内 Bleomycin 持続注入法について

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食道癌術後における上縦隔，とくに開胸反対側のとり残しリンパ節転移への対策として，胸管リンパの流れに対して逆行性または順行性に BLM を胸管内へ持続注入する方法を実験的に検討し，次のような成績を得た．

1) BLM の食道壁内局注の場合には，BLM は奇静脈血および胸管リンパ中に迅速に吸収され，さらに壁内リンパ流によって食道の頭・尾側によく広がり，所属リンパ節に高濃度に分布した．ところが上・中胸部食道を遊離後，BLM を壁内局注すると，迅速に奇静脈血中に吸収され，食道内では頭・尾側によく広がったが，所属リンパ節にはほとんど検出されず，食道壁内に大量の BLM が滞留していた．したがって，食道粘膜下へ局注された BLM が，所属リンパ節へ到達する経路としては，食道から出るリンパ管および静脈に負うところが大であり，局注された BLM が全身の血流にのって所属リンパ節へ到達する量は極めて微量であると思われた．

2) 頸部胸管へ逆行性に Lipiodol を注入すると，胸管が造影されるとともに上縦隔リンパ節が造影された．さらに経時的に胸管内圧を測定した結果，20ml 注入で胸管内圧は 40cm$H_2O$ に達するとともに，肺内へ逆流した．

3) 左頸部から気管分岐部付近の後縦隔内へ挿管し，BLM を持続注入すると，所属リンパ節内濃度は高値を示し，肺内濃度は低値にとどまった．一方食道壁内濃度は高値を示し，とくに筋層部に高く検出された．

4) 頸部胸管から逆行性に BLM を持続注入すると所属リンパ節内濃度はさらに高値を示したが，肺内濃度は後縦隔内投与群に比して差がなかった．食道内濃度も高値を示し，とくに粘膜・粘膜下層に高く検出された．

5) 胸管を左頸部および横隔膜上部で結紮し，両者のあいだの分節内へ尾側から頭側へ Lipiodol を持続注入すると弁の抵抗なく順調に胸管が造影された．Evans blue を注入した後，所属リンパ節を螢光顕微鏡下で観察した結果，大量の Evans blue の流入を認め，辺縁洞から中間洞へと進む傾向を認めた．

6) 順行性胸管内 BLM 持続注入を行うと，所属リンパ節内に大量の BLM が検出され，開胸側リンパ節郭清の後も，開胸反対側リンパ節内濃度は同様に高値を示した．

7) 頸部食道を胸骨柄で離断し，その口側を食道瘻とし，瘻壁内局注を行うと頸部所属リンパ節へ多量の BLM がとり込まれ，さらに胸部所属リンパ節にも分布した．

以上の諸成績から，BLM の順行性または逆行性胸管内持続注入法および頸部食道瘻壁内局注法は食道癌術後制癌剤療法として臨床応用しうることを実験的に確かめた．